

FGFR-selective tyrosine kinase inhibitors, such as infigratinib, show potency and selectivity for FGFR3 at pharmacologically relevant doses for the potential treatment of achondroplasia

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Background

- Germline mutations in fibroblast growth factor receptor genes 1–3 (*FGFR1–3*) can cause skeletal dysplasias and craniosynostoses.
- Mutations in *FGFR2* (e.g. *S351C*, *Y375C*, *S252W*) and *FGFR3* (e.g. *G380R*, *K650E*, *N540K*, *Y373C*) are known to cause skeletal dysplasias including craniosynostoses, short-stature syndromes such as achondroplasia and hypochondroplasia, and thanatophoric dysplasia.
- Over the past decade, several *FGFR1–3* tyrosine kinase inhibitors (TKIs), such as infigratinib (BGJ398), AZD4547, and PD173074 have been studied in a variety of preclinical models of FGFR-driven skeletal dysplasias.
- Achondroplasia is the most common form of disproportionate short stature driven by an *FGFR3* genetic alteration. It is most commonly caused by an autosomal dominant *G380R* substitution in *FGFR3*.¹
- Achondroplasia is the most frequently studied FGFR-driven skeletal dysplasia although, to date, no study has comprehensively examined the literature regarding the potential therapeutic usage of *FGFR1–3* TKIs in achondroplasia or other FGFR-driven skeletal dysplasias.

Purpose:

- Explore the publicly available literature to evaluate the dose dependency and toxicity profiles of FGFR-selective TKIs in preclinical skeletal dysplasia models.
- Evaluate, based on the comprehensive non-clinical evidence of safety and efficacy of FGFR-selective TKIs, the potential for a therapeutic option in FGFR-driven skeletal dysplasias.

Methods

- A systematic literature review was performed to investigate non-clinical data from studies of infigratinib and other FGFR-selective TKIs relevant to FGFR-driven skeletal dysplasias.
- Two major types of sources were searched on October 22/23 2019:
 - Major databases (e.g., PubMed, Medline [NLM Catalog]) were searched for relevant articles from the past 10 years.
 - Conference archives (e.g., ENDO, ESPE, ISDS, ASHG, ASBMR) were searched for relevant abstracts from the past 5 years.
- Full text was included where possible.
- Key words used in the searches included, but were not limited to, the following:
 - Achondroplasia.
 - Skeletal dysplasia.
 - FGFR inhibition.
 - Infigratinib.
 - BGJ398.
 - AZD4547.
 - PD173074.
 - Tyrosine kinase inhibitor.
- Eligibility criteria for inclusion was determined in advance to exclude content not relevant to the purpose of this literature review.

Results

- 14 publications were included in this review (Figure 1).
- 683 publications were identified through the initial search, with 326 remaining after screening for date and duplicates.
- 310 publications were excluded based on title and abstract, leaving 16 remaining to assess full text.
- Of the 16 publications reviewed as full texts, four were excluded given focus outside the scope of this literature review (e.g., focus on targets other than FGFR, discussion of therapeutic space without provision of new non-clinical data).
- Two additional publications found through reference review of identified publications were included due to direct relevance.

Figure 1. Literature review flow chart

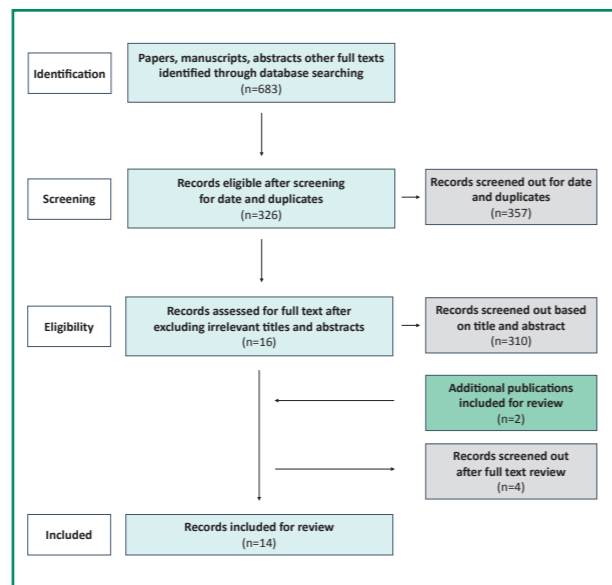
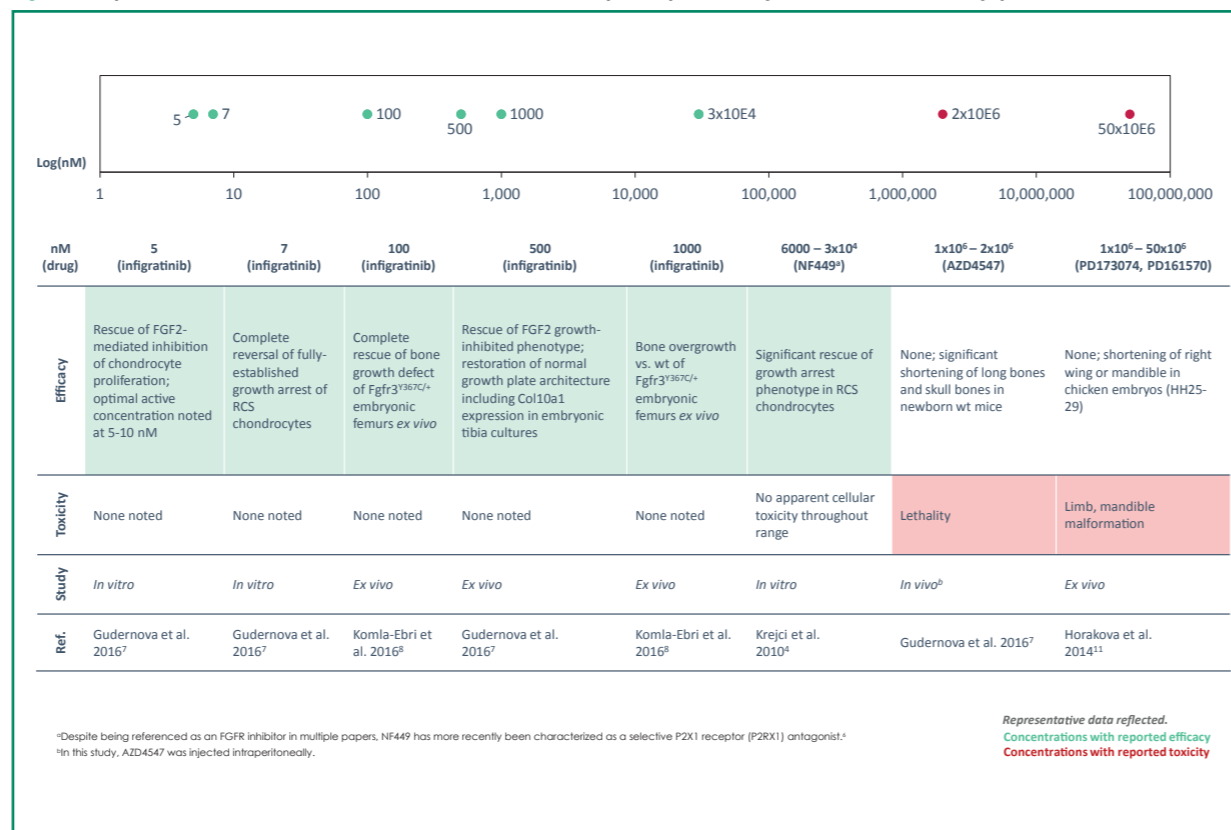
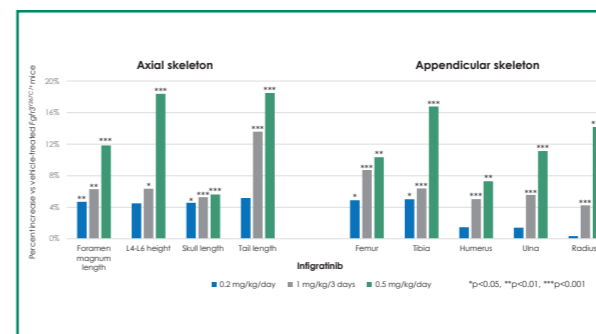


Figure 2. Representative data: concentrations of FGFR inhibitors explored preclinically in models of skeletal dysplasia



- Efficacy and toxicity findings were concentration- or dose-dependent (illustrative subset shown in Figure 2).
- FGFR-selectivity of TKIs included in this review varied, with *FGFR3* IC₅₀ ranging from 1.0 nM (infigratinib²) to 4.5 nM (ARQ 087⁹) for FGFR-selective compounds, and from 5 nM (PD173074⁴) to 190 nM (A31⁵) to 500 nM (NF449⁴) for non-selective compounds.
- Infigratinib was the most-commonly identified TKI, with eight publications on preclinical data in models of skeletal dysplasias. Key results for infigratinib show:
 - *FGFR3* IC₅₀ 1.0 nM, *FGFR3*-K650E IC₅₀ 4.9 nM.²
 - *In-vitro* data: inhibition of *FGFR1–3* activity at concentrations ranging from 5 to 500 nM, including reversal of established growth arrest in chondrocytes at 7 nM and an ‘optimal concentration’ of 5–10 nM (Figure 2).⁷
 - *Ex-vivo* data: overgrowth of ACH mouse femurs vs. WT at 1x10³ nM.⁸
 - *In-vivo* studies: dose-dependent improvements in foramen magnum and long bone length in *Fgfr3^{Y367C/+}* mice at SC doses of 0.2–2 mg/kg/day (Figure 3).^{8,9}
 - No preclinical studies reported a survival disadvantage and one showed a significant survival advantage for infigratinib-treated ACH mice (Figure 4).⁹
- In relation to other FGFR TKIs besides infigratinib:
 - Off-target biochemical effects on other RTKs were reported for most of these agents across studies, with the exception of ARQ 087, which was reported to only slightly inhibit KIT, FLT4, and TYRO3 at 500 nM (*FGFR1–3* IC₅₀ 1.8–4.5 nM).³

Figure 3. Dose response with infigratinib in an achondroplasia mouse model⁹



- *In-vitro* data show rescue of RCS cells from FGF2-mediated inhibition of proliferation at concentrations ranging from 10 nM for AZD4547 to 15 nM for PD173074.⁷
- One study of PD173074 (100 nM) showed significant rescue of primary cilia (PC) length in chondrocytes from *FGFR3^{Y367C/+}* mice to 96% of the length observed in control chondrocytes, and in human fetal TD chondrocytes to 94% of that observed in control chondrocytes.¹⁰
- *Ex-vivo* data in one study demonstrated restoration of normal growth plate architecture and ~50% growth improvement compared with controls in mouse tibia cultures treated with 1x10³ nM ARQ 087, both in the presence and absence of FGF2 (Figure 5).³
- *In-vivo* data: one study showed that AZD4547 decreased survival in newborn wild-type mice (CD1) treated at doses of 1x10⁶ to 2x10⁶ nM.⁷ Another study showed limb malformation in chicken embryos treated with PD173074 or PD161570 at doses of 1x10⁶ to 50x10⁶ nM, and increased embryo mortality above 1x10⁶ nM.¹¹

Figure 4. Survival benefit with infigratinib in an achondroplasia mouse model⁹

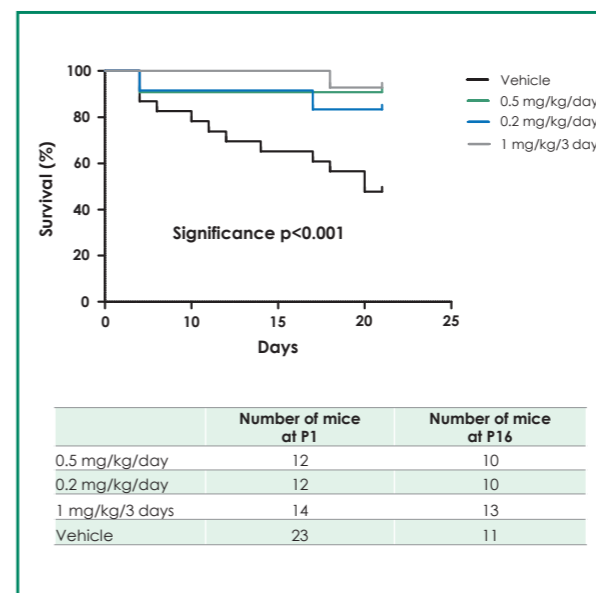
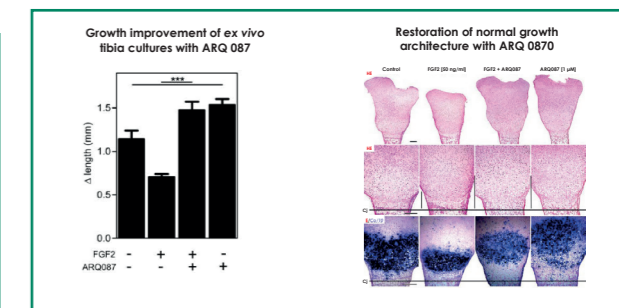


Figure 5. *Ex-vivo* improvement in tibia growth and Col10a³



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Conclusions

- While two studies suggest toxicity with FGFR-selective TKIs; this was produced at doses significantly higher than pharmacologically relevant for the treatment of achondroplasia or other skeletal dysplasias.
- In-vivo* studies in an achondroplasia mouse model treated with low doses of infigratinib showed increase in growth of long bones and foramen magnum with a good dose-response relationship. No toxic effects were observed at these low but efficacious doses.
- One study demonstrated a survival advantage in *Fgfr3^{Y367C/+}* mice treated with infigratinib.

Clinical relevance:

Given the totality of evidence, low-dose infigratinib appears to be a potentially safe option for further development in children with achondroplasia.

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